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Michael O. Leavitt, Administrator
US Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Comments on the HPV test plan for Aminoalkylnitriles Category

Dear Administrator Leavitt:

The following are comments on the test plan for Aminoalkylnitriles Category (CAS # 19355-69-2 and 4475-95-0) for the HPV program, submitted by Dupont. These comments are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health and environmental protection organizations have a combined membership of more than ten million Americans.

DuPont has grouped two HPV chemicals into the aminoalkylnitriles category, 2-amino-2-methylpropanenitrile (MPN) and 2-amino-2-methylbutanenitrile (MBN). These chemicals are produced solely by DuPont, and are produced, sampled, and transported in a completely closed process. Thus, according to the October 1999 letter agreement between EPA and program participants, toxicity endpoints are not required for repeated dose or reproductive toxicity. DuPont also utilizes data from an analogous chemical, 2-amino-2,3-dimethylbutanenitrile (DMBN), to fulfill some data endpoints, specifically repeated dose toxicity and genetic toxicity.

However, despite these measures to reduce the perceived need for testing of theses chemicals, DuPont still proposes two toxicity tests: OECD 414 and 423. This is despite acknowledging that DMBN was itself the subject of an HPV test plan first submitted by Cytec Industries, Inc. on July 20, 2001.

Data from physiochemical and environmental fate tests support the analog comparisons. The three chemicals are also all "moderately to highly toxic to aquatic life" (test plan p. 4), and all three are also extremely acutely toxic by oral, dermal, and inhalation routes, as well as extremely ocularly toxic; two of the three chemicals killed the test subjects of the ocular toxicity tests referenced.

The chemicals are less toxic when consideration is placed towards repeated-dose toxicity. Although doses were low (1.4-22 ppm via inhalation and 3-30 mg/kg via dermal administration), no adverse systemic effects were seen for either MPN or DMBN,

respectively. The authors specifically indicate that no effects were seen on any reproductive organs for either chemical or either sex.

Upon consultation of the Cytec test plan for DMBN, we found that the toxicity profile for these chemicals fits nicely with surrogates used by Cytec to recommend no testing for DMBN. Although no developmental toxicity information can be found for any of the three chemicals specifically, Cytec called upon industry knowledge that most aliphatic nitriles commonly cause developmental toxicity. Cytec cited studies investigating 10 different aliphatic nitriles, both saturated and unsaturated, using oral and inhalation routes of administration, and all resulted in adverse developmental effects on the offspring (Saillenfait and Sabate, 2000; Saillenfait et al., 1993). Cytec hypothesizes that the rapid liberation of cyanide (HCN) from aliphatic nitriles accounts for this toxicity.

Two additional studies using various aliphatic nitriles support this conclusion (Saillenfait and Sabate, 2000; Willhite et al., 1981). IP injection of two nitriles resulted in developmental defects in hamster offspring. These were prevented in all but the highest exposure group by sodium thiosulfate (a common HCN antidote) administration, leading to the speculation that liberated HCN in the maternal system is responsible for the effects. Eight other aliphatic nitriles were tested using whole embryo culture and produced concentration-dependent developmental toxicity effects on the embryos.

Cytec used this information to predict that the test chemical, DMBN, would be developmentally toxic, as these other aliphatic nitriles are known to be, and concluded that no further developmental toxicity testing was needed, especially given the extremely acutely toxic nature of the chemical and resulting current worker protection measures already in place. Furthermore, Cytec added wording to their Material Safety Data Sheet and label detailing the potential developmental effects in the event of an accidental exposure.

It is therefore puzzling and extremely distressing, given that DuPont is aware of Cytec's test plan, that the company is proposing its own developmental toxicity test. <u>This proposed test will kill at least 1300 animals.</u> We found further evidence (Froines et al., 1985) to support Cytec's conclusions and their applicability to the test plan chemicals. The release of cyanide and thiocyanide ions from aminonitriles, both *in vitro* and *in vivo*, was studied. Rat liver slices and IP injection methods were used to measure HCN and thiocyanide output; all tested animonitriles released HCN and thiocyanide *in vitro* and all but two did so *in vivo*. This study addresses previous commentators' concerns regarding the amino group on aliphatic nitriles in the Cytec and DuPont test plans and whether it would affect the chemicals' toxicity profiles. At the very least, perhaps DuPont could conduct a similar *in vitro* study to determine whether the aminonitriles in question in this test plan in fact release HCN; if so, the perceived need for a developmental toxicity study will be further obviated. We urge DuPont to consider all toxicological evidence and options for action available to them before committing to the killing of 1300 animals to check this box in the SIDS data set.

We also urge DuPont to use human or immortalized non-human animal cells for the chromosomal aberration test, if in fact no suitable animonitrile surrogates can be found to fulfill this testing endpoint.

Thank you for your attention to this issue. I look forward to a prompt and favorable response to our concerns. I can be reached at 202-686-2210 ext. 335 or via email at kstoick@pcrm.org.

Sincerely,

Kristie Stoick, MPH
Research Analyst

Chad B. Sandusky, PhD
Director of Research

Citations

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